

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-833

CHEMISTRY REVIEW(S)

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-833

CHEM. REVIEW #:

REVIEW DATE: 28-SEP-00

3

<u>SUBMISSION</u> <u>TYPE</u>	<u>DOCUMENT</u> <u>DATE</u>	<u>CDER DATE</u>
Original	30-MAR-98	31-MAR-98
Amendment	29-APR-98	01-MAY-98
Amendment	27-MAY-98	28-MAY-98
Amendment	22-DEC-98	23-DEC-98
Amendment	07-JUN-99	08-JUN-99
Amendment	10-JUN-99	14-JUN-99
Amendment	30-JUN-99	02-JUL-99
Amendment*	30-MAR-00	31-MAR-00
Amendment*	06-SEP-00	07-SEP-00
Amendment*	07-SEP-00	08-SEP-00
Amendment*	14-SEP-00	15-SEP-00
Amendment*	20-SEP-00	21-SEP-00
Amendment*	27-SEP-00	
Amendment*	28-SEP-00	

*Subject of this
review

NAME & ADDRESS OF
APPLICANT:

DRUG PRODUCT NAME:

Flovent Diskus

Proprietary:

Nonproprietary/USAN:

Fluticasone propionate inhalation powder

Code Name/#:

Chem. Type/Ther. Class:

3S

PHARMACOL.

Glucocorticoid/bronchial asthma

CATEGORY/INDICATION

DOSAGE FORM:

Powder

CR#3

STRENGTHS:50, 100, 250 mcg; 28 and 60 blisters/device;
target emitted dose: 47, 94, and 235 mcg.**ROUTE OF ADMINISTRATION:**

Inhalation

DISPENSED:☒ Rx ☐ OTC**SPECIAL PRODUCTS:**☐ YES ☒ NO(If yes, fill out the form for special products and deliver to
the TIA through the team leader for data entry)**APPEARS THIS WAY
ON ORIGINAL****APPEARS THIS WAY
ON ORIGINAL****APPEARS THIS WAY
ON ORIGINAL**

CR#3

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:**

See USAN

SUPPORTING DOCUMENTS:**DMFs**

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Reviews
			Adequate	16-AUG-99	See under _____
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#5, NDA 20-692
			Adequate		See under _____
			Adequate	20-JAN-00	CR#1 of NDA 20-833 See CR#3, Evaluation of Question 5.a.

RELATED DOCUMENTS (if applicable)

Type Number	Owner	Subject	
NDA 21-121	GlaxoWellcome	Flonase Nasal Spray	Approved
NDA 20-548	GlaxoWellcome	Flovent Inh. Aerosol	Approved
NDA 19-957	GlaxoWellcome	Cutivate Ointment	Approved
NDA 19-958	GlaxoWellcome	Cutivate Ointment	Approved
NDA 20-549	GlaxoWellcome	Flovent Rotadisk Inh. Pow.	Approved

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER		AC	Recommendation dated 05-MAY-00.
Microbiology, HFD-160	Not applicable.		
Biometrics, HFD-715		Done.	Consult review dated 28-SEP-00. See review below.
Environmental Assessment	Not applicable.		The firm has requested a categorical exclusion based upon 21 CFR 25.31(b). (see review of submission dated 27-SEP-00 in CR#3). This is

CR#3

			acceptable.
Pharm./Tox.	02-NOV-99; qualification of mouthpiece colorant	Accept.	Pharm/tox consult review dated 21-SEP-00 by Larry Sancilio
Labeling & Nomenclature Committee	Not applicable.		

REMARKS:

1. For the sake of easy reference, the drug substance specifications (from attachment I of CR# 2) are included in **attachment I** to this review and the lactose specifications (from the submission dated 27-SEP-00) included in **attachment II** to this review. The drug substance specifications were found acceptable in CR# 2, evaluation of FDA Question 2. The lactose specifications were found acceptable in CR# 3.
2. Note that information concerning the _____ used as one of the _____ for the drug product is provided in the NDA rather than referenced to a DMF (see CR#1, page 47).
3. The NDA is not being approved for once-daily dosing due to clinical and _____ concerns (see Questions 1 and 2 in review). Due to concerns with stability
4. The NDA is being approved with the following expiration dating periods and in use periods (see Evaluation of 7.b. below:

<u>STRENGTH</u>	<u>EXP. DATING PERIOD</u>	<u>IN USE PERIOD</u>
50 UG	18 MONTHS	6 WEEKS
100 UG	18 MONTHS	2 MONTHS
250 UG	24 MONTHS	2 MONTHS

5. Acknowledgement of the following commitments should be included with the final action on the application.

We acknowledge your commitments:

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CONCLUSIONS AND RECOMMENDATIONS:

From a chemistry, manufacturing, and controls perspective, it is recommended that the application be approved. Acknowledgement of commitments made by the applicant should be included in the approval letter; see under REMARKS section above.

**APPEARS THIS WAY
ON ORIGINAL**

cc:

Orig. NDA : 20-833

HFD-570/Division File

HFD-570/DKoble

HFD-570/SBarnes

HFD-570/GPoochikian

HFD-570/MPurucker

R/D Init. by: **/S/** 7/28/00

filename: NDA20833.cr3.doc

/S/

Dale L. Koble, Ph.D., Review Chemist

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DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-833

CHEM. REVIEW :
Addendum U CR#2

REVIEW DATE:
07-DEC-99

<u>SUBMISSION</u> <u>TYPE</u>	<u>DOCUMENT</u> <u>DATE</u>	<u>CDER DATE</u>
Original	30-MAR-98	31-MAR-98
Amendment	29-APR-98	01-MAY-98
Amendment	27-MAY-98	28-MAY-98
Amendment	22-DEC-98	23-DEC-98
Amendment*	07-JUN-99	08-JUN-99
Amendment*	10-JUN-99	14-JUN-99
Amendment*	30-JUN-99	02-JUL-99

*Subject of this
review —

NAME & ADDRESS OF
APPLICANT:

DRUG PRODUCT NAME:

Proprietary:

Nonproprietary/USAN:

Code Name/#:

Chem. Type/Ther. Class:

PHARMACOL.

CATEGORY/INDICATION

Flovent Diskus

Fluticasone propionate inhalation powder

3S

Glucocorticoid/bronchial asthma

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

DISPENSED:

SPECIAL PRODUCTS:

(If yes, fill out the form for special products and deliver to
the TIA through the team leader for data entry)

Powder

50, 100, 250 mcg; 28 and 60 blisters/device;
target emitted dose: 47, 94, and 235 mcg.

Inhalation

☒ Rx

☐ OTC

☐ YES

☒ NO

Page 2

cc:

Orig. NDA : 20-833

HFD-570/Division File

HFD-570/DKoble

HFD-570/LCobbs

HFD-570/GPoochikian

HFD-570/MPoorer

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filename: ADDEDNUMNDA20833.cr2.doc/S/

12/7/99

Dale L. Koble, Ph.D., Review Chemist

REMARKS

The attached draft comments should be included in the not approvable letter to the applicant in the stability section of the comments (add as "e" to comment 5 in the comments from CR#2 dated 23-NOV-99).

**APPEARS THIS WAY
ON ORIGINAL**

2 Page(s) Withheld

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NOV 28 1999

NDA #: 20-833

CHEM. REVIEW #:

2

REVIEW DATE:

23-NOV-99

<u>SUBMISSION</u> <u>TYPE</u>	<u>DOCUMENT</u> <u>DATE</u>	<u>CDER DATE</u>
Original	30-MAR-98	31-MAR-98
Amendment	29-APR-98	01-MAY-98
Amendment	27-MAY-98	28-MAY-98
Amendment	22-DEC-98	23-DEC-98
Amendment*	07-JUN-99	08-JUN-99
Amendment*	10-JUN-99	14-JUN-99
Amendment*	30-JUN-99	02-JUL-99

*Subject of this
review

NAME & ADDRESS OF
APPLICANT:

DRUG PRODUCT NAME:

Flovent Diskus

Proprietary:

Nonproprietary/USAN:

Fluticasone propionate inhalation powder

Code Name/#:

Chem. Type/Ther. Class:

3S

PHARMACOL.

Glucocorticoid/bronchial asthma

CATEGORY/INDICATION

DOSAGE FORM:

Powder

STRENGTHS:

50, 100, 250 mcg; 28 and 60 blisters/device;
target emitted dose: 47, 94, and 235 mcg.

ROUTE OF ADMINISTRATION:

Inhalation

DISPENSED:

☒ Rx ☐ OTC

SPECIAL PRODUCTS:

☐ YES ☒ NO

(If yes, fill out the form for special products and deliver to
the TIA through the team leader for data entry)

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:**

See USAN

SUPPORTING DOCUMENTS:**DMFs**

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Reviews
			Adequate	16-AUG-99	See under _____
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#5, NDA 20-692
			Adequate		See under _____ CR#1 of NDA 20-833
			Inadequate	24-NOV-99	See CR#2, Evaluation of Question 7

RELATED DOCUMENTS (if applicable)

Type Number	Owner	Subject	
NDA 21-121	GlaxoWellcome	Flonase Nasal Spray	Approved
NDA 20-548	GlaxoWellcome	Flovent Inh. Aerosol	Approved
NDA 19-957	GlaxoWellcome	Cutivate Ointment	Approved
NDA 19-958	GlaxoWellcome	Cutivate Ointment	Approved
NDA 20-549	GlaxoWellcome	Flovent Rotadisk Inh. Pow.	Approved

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	28-MAY-98		Should be checked by CSO.
Microbiology, HFD-160	N/A		
Biometrics, HFD-710	N/A		
Environmental Assessment	N/A		
Pharm./Tox.	02-NOV-99; qualification of _____	pending	
Labeling & Nomenclature Committee	N/A		

REMARKS:

1. Prior to taking an action on the NDA, the project manager/CSO should:
 - Check on the EIR
 - Include any comments from pharm/tox on the _____
2. Note that information concerning the _____ used as _____ for the drug product is provided in the NDA rather than referenced to a DMF (see CR#1, page 47).
3. The draft patient instructions for use of the device (Original NDA, Vol. pages 56-60) closely follows that for Serevent Diskus. The mock up labeling should be checked for consistency with Serevent Diskus.

Note that the proposed instructions for Ventolin Diskus (Original NDA 21-034, Vol. 1, pages 51-53) are significantly different from that for Serevent Diskus.

4. Item 4008/97 was reviewed as the _____ (DMF —) although no LOA was provided in NDA 20-833. An LOA was provided for this item in the related NDA 21-034 (Ventolin Diskus).

CONCLUSIONS AND RECOMMENDATIONS:

From a chemistry, manufacturing, and controls perspective, it is recommended that the application be considered not approvable. The attached draft comments should be sent to the applicant.

cc:

Orig. NDA : 20-833

HFD-570/Division File

HFD-570/DKoble

HFD-570/LCobbs

HFD-570/GPoochikian

HFD-570/MPurucker

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Dale L. Koble, Ph.D., Review-Chemist

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MAR 26 1999

DIVISION OF PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-833

CHEM. REVIEW #:

1

REVIEW DATE:

25-MAR-99

<u>SUBMISSION</u> <u>TYPE</u>	<u>DOCUMENT</u> <u>DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	30-MAR-98	31-MAR-98	
Amendment	29-APR-98	01-MAY-98	
Amendment	27-MAY-98	28-MAY-98	
Amendment	22-DEC-98	23-DEC-98	

NAME & ADDRESS OF
APPLICANT:

DRUG PRODUCT NAME:

Flovent Diskus

Proprietary:

Nonproprietary/USAN:

Fluticasone propionate inhalation powder

Code Name/#:

Chem. Type/Ther. Class:

3S

PHARMACOL.

Glucocorticoid/bronchial asthma

CATEGORY/INDICATION

DOSAGE FORM:

Powder

STRENGTHS:

50, 100, 250 mcg; 28 and 60 blisters/device;
target emitted dose: 47, — and — mcg.

ROUTE OF ADMINISTRATION:

Inhalation

DISPENSED:

☒ Rx ☐ OTC

SPECIAL PRODUCTS:

☐ YES ☒ NO

(If yes, fill out the form for special products and deliver to
the TIA through the team leader for data entry)

**APPEARS THIS WAY
ON ORIGINAL**

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:**

See USAN

SUPPORTING DOCUMENTS:**DMFs**

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in Reviews
			Inadequate	05-FEB-99	See under
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#4, NDA 20-692
			Adequate		See CR#4, NDA 20-692
			Adequate		See under CR#1 of NDA 20-833

RELATED DOCUMENTS (if applicable)

Type Number	Owner	Subject	
NDA 21-121	GlaxoWellcome	Flonase Nasal Spray	Approved
NDA 20-548	GlaxoWellcome	Flovent Inh. Aerosol	Approved
NDA 19-957	GlaxoWellcome	Cutivate Ointment	Approved
NDA 19-958	GlaxoWellcome	Cutivate Ointment	Approved
NDA 20-549	GlaxoWellcome	Flovent Rotadisk Inh. Pow.	Approved

CONSULTS:

CONSULT	DATE FORWARDED	STATUS	COMMENTS
EER	28-MAY-98		Should be checked by CSO.
Microbiology, HFD-160	N/A		
Biometrics, HFD-710	Deferred; updated stability on drug product is being requested.		
Environmental Assessment	N/A		
Labeling & Nomenclature Committee	N/A		

APPEARS THIS WAY
ON ORIGINAL

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cc:

Orig. NDA : 20-833

HFD-570/Division File

HFD-570/DKoble

HFD-570/LCobbs

HFD-570/GPoochikian

HFD-570/MPinnerker

R/D Init. by: /S/ 126/99

filename: NDA20833.cr1.doc

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3/-5/99

Dale L. Koble, Ph.D., Review Chemist

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ON ORIGINAL

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**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 20833/000 Stamp: 31-MAR-1998 Regulatory Due: 30-SEP-2000 Applicant: GLAXO 5 MOORE DR RESEARCH TRIANGLE PARK, NC 27	Priority: 3S Action Goal: Brand Name: FLOVENT DISKUS (FLUTICASONE PROPIONATE) Established Name: Generic Name: FLUTICASONE PROPIONATE INHALATION POWDER Dosage Form: AER (AEROSOL) Strength: 50, 100, AND 250 UG
FDA Contacts: D. KOBLE (HFD-170) G. POOCHIKIAN (HFD-570)	301-827-7428 , Review Chemist 301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 05-MAY-2000 by M. GARCIA (HFD-322) 301-594-0095
ACCEPTABLE on 17-AUG-1999 by M. GARCIA (HFD-322) 301-594-0095
WITHHOLD on 30-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **9610411**
GLAXO OPERATIONS UK LTD

WARE, HERTFORDSHIRE, UK

DMF No:
AADA No:

Profile: **ADM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE**
FINISHED DOSAGE
MANUFACTURER

Establishment: **9610421**
GLAXO WELLCOME LTD
DL128DT
BARNARD CASTLE, , UK

DMF No:
AADA No:

Profile: **CTI** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE STABILITY**
TESTER

Establishment: **9610414**
GLAXO WELLCOME OPERATIONS U
DA1 5AH
DARTFORD, KENT, UK

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT


Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

Establishment: **9611905**
LABORATOIRES GLAXO
27000
EVREUX, CEDEX, FR

DMF No:
AADA No:

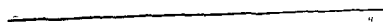
Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE**

Establishment: 

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

Responsibilities: 

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9617236**
GLAXO WELLCOME SPAIN SA
CALLE DR SEVERO OCHOA
TRES CANTOS, MADRID, SP 28760

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE STABILITY
TESTER**

Establishment: **9610419**
GLAXOCHEM LTD
COBDEN ST
MONTROSE ANGUS, SCOTLAND, UK

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **30-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: _____

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

Responsibilities: _____

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

TESTER


Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: **9611905**
LABORATOIRES GLAXO
ZONE INDUSTRIELLE 2 27000
EVREUX, CEDEX, FR

DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE**

Establishment: 

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **29-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: _____

**APPEARS THIS WAY
ON ORIGINAL**